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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,580	01/18/2001	John C. Smith	P 0276522 PHM.70640/US	4676

7590 10/03/2002

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EXAMINER
EINSMANN, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	18

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/761,580	SMITH ET AL.	
	Examiner	Art Unit	
	Juliet C Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2002 and 16 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *3-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-2 in Paper No. 8 and paper number 12 is acknowledged. The traversal is on the ground(s) that it would not put an undue burden of search on the Examiner to consider all of the polymorphisms together since all of the recited polymorphisms are found in the same gene or encoded protein. This is not persuasive because each of these polymorphisms represents a distinct structural entity that has different effects on the encoded polypeptide or represents a different variant of the polypeptide itself. The methods for detection of the polymorphisms must each be evaluated under each statue for prior art as well as issues under 112 1st, 2nd and 101. Each polymorphism, or combination of polymorphisms is thus a distinct invention requiring separate search and consideration that would be a burden to the examiner. Applicant further argues that the methods for detection of the polymorphism in the nucleic acid and the protein should be examined together since the same polymorphism can be detected in nucleic acids and proteins. This is not found persuasive because although both inventions involve the detection of polymorphism, the detection of a polymorphism in proteins and nucleic acids involves the use of different methodologies. Searches required to examine the two types of methodologies would be different, requiring a search of different classes, different electronic databases and the use of different key words in such a search.

Finally, applicant points out that the claims cover determining the sequence at one or more of the four positions and that if the restriction requirement is allowed to stand it will limit applicants to claiming methods for determining the sequence at only one of the positions. This is

not persuasive, nor is it necessarily accurate. Claims which particularly require the examination of more than one polymorphic site were not presented. The claims, as presented and restricted, only **require** the examination of a single polymorphic site, and as such the restriction remains proper. As such, the restriction requirement is still deemed proper.

The requirement is still deemed proper and is therefore made FINAL.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Detection of Polymorphisms in the Human Pyruvate Dehydrogenase Complex E2 Gene.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 are indefinite over the recitation "determining the sequence of the nucleic acid of the human at one or more of positions..." because it is unclear how you determine a sequence at a single position of a nucleic acid. The word "sequence" implies the determination of the nucleotide present at more than one position of a nucleic acid, yet the claim sets forth that the sequence is determined at one or more of the recited positions. It is not clear how a sequence

can be determined at a particular position. Amendment of the claim to recite, for example, "determination of the nucleotide present at position 1255 of SEQ ID NO: 1" would obviate this rejection.

Claims 1 and 2 are further indefinite over the recitation "determining the status of the human by reference to polymorphism" because it is not clear what this step is requiring. It is not clear what it means to determine the status of a human "by reference to polymorphism."

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting and sequencing the human pyruvate dehydrogenase complex E2 (PDH E2) gene and portions thereof, does not reasonably provide enablement for methods which are limited to the detection of a polymorphism at position 1255 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention commensurate in scope with these claims.

This rejection applies to the instant claims insofar as they might be interpreted as methods for the detection of the presence or absence of particular single nucleotide polymorphisms. Insofar as the instant claims read generally on methods for sequencing the human pyruvate dehydrogenase complex E2 (PDH E2) gene, this rejection does not apply (see prior art rejections herein). The teachings of the specification (at, e.g., page18) and of the prior art as exemplified by Thekkumkara et al. disclose methods of detecting and sequencing the PDH

E2 gene and portions thereof. Such methods are encompassed by the instant claims as written, and a person skilled in the art could clearly practice methods of detecting and sequencing a known gene without further guidance. However, it is unpredictable as to whether one of skill in the art could use without undue experimentation methods requiring detection of the polymorphism at position 1255 of SEQ ID NO: 1, which methods are also encompassed by the claims.

It is noted that the instant claims each recite methods which comprise the detection of nucleotide sequences at one or more of four different polymorphic sites. A restriction requirement was set forth in which applicant was required to select a single polymorphic site for examination. Applicant selected the polymorphism at position 1255 of SEQ ID NO: 1. This enablement rejection considers only this site in the claim.

The instant claims are drawn to methods for the diagnosis of a polymorphism in an PDH E2 gene in a human. The methods comprise steps in which the particular nucleotide present is detected at a particular position in SEQ ID NO: 1.

The specification teaches that the PDH E2 gene has been associated with a number of diseases and physiological states (pages 1-3). Further, the specification provides two polymorphisms in the PDH E2 gene. In particular, the specification teaches a polymorphic site at position 1255 of SEQ ID NO: 1, and that this particular polymorphism results in an amino acid change in the encoded polypeptide (ASP349ASN). The specification is silent with respect to the effect of this polymorphism on the biological activity of the encoded polypeptide, and beyond the fact that the polymorphism causes a change in the encoded polypeptide, the specification is silent with respect to the effect of this polymorphism on the PDH E2 gene. The specification

does not disclose any relationship between the presence of this polymorphism and any particular disease state or physiological condition.

The prior art provides polymorphisms in the PDH E2 gene. Leung et al. (Autoimmunity (1993) 14(4) 335-40) teach a Taq I polymorphism found in both patients with biliary cirrhosis and in control patients. It is not clear if this polymorphism is identical to the instantly disclosed polymorphism, although it appears it may be (see prior art rejections set forth under 102(b)). Moehario et al. teach polymorphisms in the ClaI region of the gene (Biochimica et Biophysica Acta, 1097 (1991) 128-132). Neither of these provide specific guidance with regard to the polymorphism identified herein as being at position 1255 of SEQ ID NO: 1.

There is also a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where

multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different polymorphisms in the PDH E2 gene, it remains highly unpredictable as to the biological significance of these polymorphisms. Thus, the claimed method directed towards the diagnosis of polymorphisms, or the diagnosis or prognosis of disease via detection of polymorphisms, for enablement of the full scope, requires the knowledge of unpredictable and potentially non-existent associations between the instantly elected polymorphism and some phenotypic trait. Even if the elected polymorphism is in some way associated with some disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the PDH E2 gene.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. With regard to claims directed towards simple detecting the presence of the gene polymorphism, applicant speculates that these polymorphisms "may help to identify patients most suited to therapy with particular pharmaceutical agents (specification, page 3)." However, since the effects of any given polymorphism on gene activity are highly unpredictable, it is impossible to predict from the teachings of the instant specification what identifications can be made using the instantly claimed methods. That is, the specification does not provide any guidance as to how the polymorphism at position 1255 of SEQ ID NO: 1 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug. Furthermore, with regard to methods that particularly recite the diagnosis or prognosis of disease, the specification does not provide any guidance, other than the suggestion that these methods could be carried out for "PDH E2 mediated diseases." The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed polymorphic site as a marker for any disease in particular, or for disease in general.

The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention, one would have to establish a relationship between the polymorphism at nucleotide 1255 of SEQ ID NO: 1 some physiological or disease state. Indeed, even to use the method of claim 1 to identify patients suited for particular pharmaceutical agents, one would need to know that the polymorphism at nucleotide 1255 of SEQ ID NO: 1 was in some way associated with response to some pharmaceutical agent. In order to obtain the type of information necessary to practice the claimed invention, one would be

required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in disease detection and/or treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the G/A polymorphism at position 1255 and any disease or condition. Further, absent a teaching the G/A polymorphism at position 1255 is not associated with such conditions, it is further unpredictable as to whether detection of the G/A polymorphism at position 1255 would be useful in predicting, e.g., the absence or decreased likelihood of such conditions.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention, it is concluded that undue experimentation would be required to use the instantly claimed invention. Thus, with respect to claims 1-2, although the specification certainly enables one to detect the presence of the polymorphism (i.e. the "make" portion of 112 1st paragraph), it would require undue experimentation in order to determine how to use the methods of claims 1-2. Considering all of the factors discussed herein, it is concluded that it would require undue experimentation to determine the particular disease state that can be diagnosed and thus to practice the claimed invention commensurate in scope with the present claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Thekkumkara et al. (FEBS Letters, November 1988, Vol. 240, number 1,2, pages 45-48).

Thekkumkara et al. teach a method for the diagnosis of a polymorphism in an PDH E2 gene in a human which comprises determining the sequence of the nucleic acid of the human at position 1255 of SEQ ID NO: 1, and determining the status of the human by reference to polymorphism in the PDH E2 gene (p. 45 and FIG. 2). Specifically, Thekkumkara et al. teach a method for sequencing the mRNA that encodes the PDH E2 gene (p. 45). At least nucleotides Nucleotides 800-1800 of the sequence taught by Thekkumkara et al. are identical to nucleotides 800-1800 of instant SEQ ID NO: 1, thus encompassing the position 1255 of SEQ ID NO: 1. This reference is considered to teach the invention of claims 1 and 2 because the method contains only two method steps, one in which the sequence at position 1255 of SEQ ID NO: 1 is determined (i.e. which is inherently accomplished by sequencing the portion of the gene that overlaps with position 1255 of SEQ ID NO: 1), and one in which the "status of the human by reference to polymorphism" is determined. Determining the sequence of the gene is considered to inherently determine the status of the human by reference to the polymorphism because by sequencing the nucleotide present at position 1255, the status of the polymorphism is determined.

9. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al. (Autoimmunity, 1993, Vol. 14, pp. 335-340).

Leung et al. teach a method for the diagnosis of a polymorphism in an PDH E2 gene in a human which comprises determining the sequence of the nucleic acid of the human at position 1255 of SEQ ID NO: 1, and determining the status of the human by reference to polymorphism in the PDH E2 gene (p. 45 and FIG. 2). Specifically, Leung et al. teach a method for the diagnosis of a polymorphism in a PDH E2 gene wherein the restriction enzyme TaqI is used to identify a polymorphism in the gene.

The restriction endonucleiase TaqI recognizes the sequences 5′ ... T^C G A ... 3′ or the sequence 3'...A G C^T... 5′. The polymorphism herein disclosed at position 1255 of SEQ ID NO: 1 results in a TaqI restriction site when a "g" is present at 1255, and the absence of a TaqI restriction site when an "a" is present at 1255. Thus, Leung et al. inherently teach a method which determines the sequence at position 1255 of SEQ ID NO: 1 via RFLP analysis.

Applicant is reminded that MPEP 2112.01 teaches "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.'" In the instant case, the method of the prior art is substantially identical to the instantly claimed method. The fact that the instant polymorphism results in a TaqI site and the polymorphism disclosed by Leung et al. is a TaqI polymorphism is believed to be a sound basis for believing that the

polymorphism disclosed herein is identical to the polymorphism disclosed by Leung et al. As such, the method for detecting the polymorphism taught by Leung et al. inherently meets the limitations of the instantly rejected claims.

Conclusion

10. No claims are allowed.

11. A rejection for lack of utility under 101 has not been applied to claims 1-2 because these claims encompass an embodiment that would have utility, namely the sequencing of the PDH E2 gene, which itself is known to be associated with physiological and disease states (see specification, page 1). If the claims are narrowed to exclude this embodiment, these claims may be subject to such rejections.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Einsmann
Examiner
Art Unit 163434

September 16, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600